CH-Activation of *L*-Proline analogues

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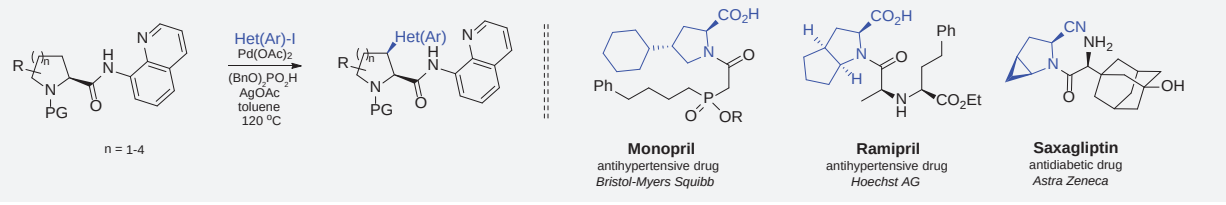
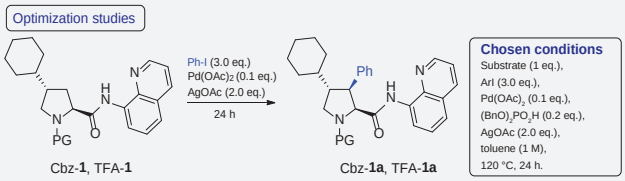
Introduction and Aim

Saturated azaheterocycles are at the heart of modern drug discovery.[1-10] In particular, substituted analogues and homologues of *L*-Proline frequently occur in the structure of the marketed drugs. *L*-Proline and its analogues possess unique conformational properties of the *N*-amide bond. Substituted prolines are intrinsically conformationally restricted, 3D-shaped and have a high fraction of sp^3 centers (Fsp^3). In this context, the development of practical synthetic approaches to these molecules is in high demand among pharmaceutical companies.

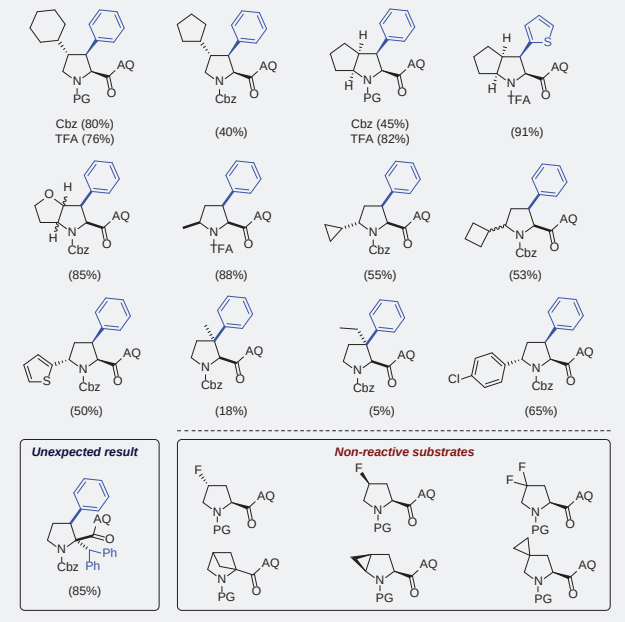


Synthesis

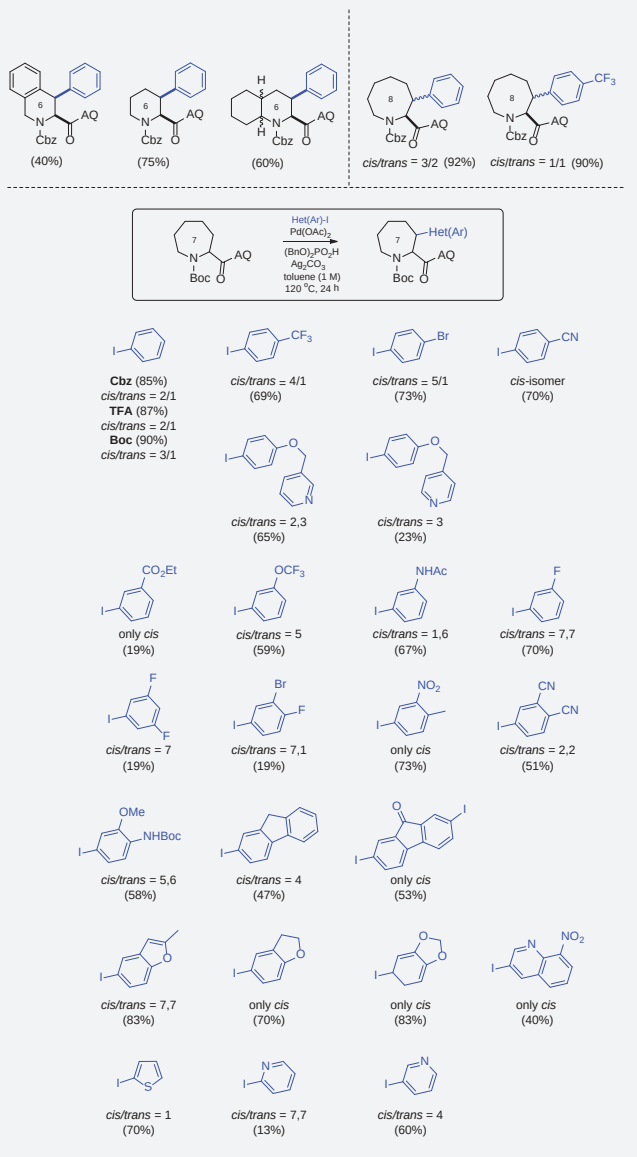


Substrate	Solvent	Temp.	Add (0.2 eq.)	Conversion (LC-MS)
Cbz – 1	-	110 °C	-	86%
	DCE	110 °C	-	56%
	Toluene	110 °C	-	69%
Cbz - 1	-	130 °C	-	84%
	DCE	130 °C	-	81%
	Toluene	130 °C	-	94%
Cbz - 1	Toluene	120 °C	PivOH	83%
	Toluene	120 °C	**$(BnO)_2PO_2H$**	**100%**
	Toluene	120 °C	**BINOL-PO_2H**	**100%**
TFA - 1	Toluene	120 °C	PivOH	76%
	Toluene	120 °C	**$(BnO)_2PO_2H$**	**100%**
	Toluene	120 °C	BINOL-PO_2H	85%

Results – proline derivatives



Results – ring size enlargement



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